Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 38, No. 4, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01513-3

Prognostic Value of Serum Cardiac Troponin I in Ambulatory Patients With Chronic Renal Failure Undergoing Long-Term Hemodialysis

A Two-Year Outcome Analysis

Ijaz A. Khan, MD, FACC,* Norrapol Wattanasuwan, MD,† Nirav J. Mehta, MD,* Aung Tun, MD, FACC,† Narpinder Singh, MD,† Harinder K. Singh, MD,† Balendu C. Vasavada, MD, FACC,† Terrence J. Sacchi, MD, FACC†

Omaha, Nebraska and Brooklyn, New York

OBJECTIVES We sought to evaluate the prognostic value of cardiac troponin I (cTnI) in asymptomatic, ambulatory patients with chronic renal failure treated with long-term hemodialysis.

BACKGROUND Smaller, short-term follow-up studies on this subject have given conflicting results.

METHODS A total of 126 ambulatory patients with chronic renal failure treated with long-term hemodialysis were followed for two years for all-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions. Serum cTnI was measured before dialysis at the time of study entry.

RESULTS One hundred two patients had normal serum levels of cTnI (≤0.03 ng/ml) and 24 patients had elevated levels (0.015 ± 0.007 vs. 0.053 ± 0.029 ng/ml, $p < 0.0001$). No significant difference in all-cause mortality (20 vs. 4 deaths), cardiac mortality (4 vs. 1 death), all-cause hospital admissions (1.74 ± 1.72 vs. 1.25 ± 1.19 admissions/patient) or cardiac admissions (0.52 ± 0.89 vs. 0.33 ± 0.76 admissions/patient) was present between the patients with normal cTnI levels and those with elevated cTnI levels. Serum cTnI was not significantly different between patients who died versus those who survived (0.022 ± 0.019 vs. 0.022 ± 0.021 ng/ml). Serum cTnI was not an independent predictor of all-cause mortality, cardiac mortality, all-cause admissions or cardiac admissions. Age (older) and serum albumin (lower) were independent predictors of all-cause mortality, whereas a history of myocardial infarction was an independent predictor of cardiac mortality. Serum sodium (lower) was an independent predictor of all-cause hospital admissions, whereas hypertension and previous myocardial infarction were independent predictors of cardiac admissions. The best predictors of the time to death were age (older) and serum sodium level (lower), irrespective of the serum cTnI levels.

CONCLUSIONS Cardiac troponin I has a limited role in predicting mortality and hospital admissions in asymptomatic patients with chronic renal failure treated with long-term hemodialysis. (J Am Coll Cardiol 2001;38:991–8) © 2001 by the American College of Cardiology

The cardiac troponins have emerged as sensitive and specific markers to detect myocardial injury and infarction, facilitating rapid bedside diagnosis and early risk stratification (1–6). In addition to detecting acute myocardial infarction, cardiac troponin I (cTnI) and cardiac troponin T (cTnT) may identify high-risk patients with cardiac diseases who tend to have subsequent cardiac-related events (7,8). Coronary artery disease is highly prevalent in patients with

See page 999

end-stage renal disease and accounts for much of their observed morbidity and mortality; 50% of patients with end-stage renal disease die of cardiovascular events (9). Diagnosing ischemic heart disease in this patient population remains challenging, because many of these patients present with abnormal baseline electrocardiograms, frequently compounded by silent or atypical symptoms and a reduced reliability of creatine kinase-MB isoenzyme (CK-MB), the conventional marker of myocardial necrosis (9–14). Several studies have questioned the usefulness of the cardiac troponins, particularly cTnT, in the presence of renal disease (14–22).

Because cTnI is exclusively of cardiac origin and, unlike CK-MB and cTnT, does not express in the skeletal muscle at any developmental stage, it has been shown to be more specific for the detection of myocardial injury in patients with chronic renal failure (14–16,23–28). However, the prognostic value of elevated serum cTnI to predict subsequent cardiac-related events in asymptomatic patients with renal disease treated with hemodialysis has not been extensively studied with long-term follow-up; the subject has only been studied with follow-up periods limited to 6 to 12 months (29–31). The present study was conducted to evaluate the prognostic value of elevated cTnI in asymp-

From the *Division of Cardiology, Department of Medicine, Creighton University School of Medicine, Omaha, Nebraska; and †Long Island College Hospital, Brooklyn, New York.

Manuscript received January 30, 2001; revised manuscript received May 21, 2001, accepted June 28, 2001.

JACC Vol. 38, No. 4, 2001
October 2001:991–8

Abbreviations and Acronyms

CK-MB = creatine kinase-MB isoenzyme
cTnI = cardiac troponin I
cTnT = cardiac troponin T
ECG = electrocardiogram or electrocardiographic
ROC = receiver-operating characteristic

tomatic, ambulatory patients with chronic renal failure treated with long-term hemodialysis. The follow-up period extended to two years.

METHODS

Patients. The study was approved by the Institutional Review Board for Human Subjects Research of the Long Island College Hospital. Written, informed consent was received from all of the participants. A total of 128 consecutive ambulatory patients with chronic renal failure undergoing long-term hemodialysis in the Hemodialysis Unit of the Long Island College Hospital were included in the study. The minimal duration of hemodialysis was one year. Exclusion criteria were: 1) acute coronary syndrome within three months; 2) chronic stable angina pectoris; 3) chest pain in the peridialysis period or during four weeks before enrollment; 4) recent major cardiovascular surgery; and 5) significant electrocardiographic (ECG) changes suggestive of myocardial injury or ischemia. The patients were evaluated by a complete medical history and physical examination, and 12-lead ECGs were recorded. Blood samples were drawn before dialysis on the patients' routinely scheduled hemodialysis day within a three-day time frame. All patients denied having chest pain at the time their blood was drawn. Cardiac troponin I, CK-MB, blood urea nitrogen, creatinine, calcium, potassium, sodium, albumin, bicarbonate and chloride levels were measured from all blood samples.

Assays. All of the serum samples were centrifuged for 5 min at 2,300 revolutions per minute to remove any particulate matter. Plunger-type filters were used to remove any remaining fibrin. Each tube was labeled with the patient number and accession number. The technicians who performed the assays were had no knowledge of the clinical data. Specimens were re-analyzed at random or to verify an abnormal result to eliminate technical errors. Collected data were summarized on spreadsheets, with the data sorted in ascending order by both the patient number and accession number.

Cardiac troponin I was measured with the ACCESS troponin I assay (Sanofi Diagnostic Pasteur, Chaska, Minnesota). The ACCESS troponin I assay is a two-site sandwich immunochemiluminescent assay using two mouse monoclonal antibodies as captured and labeled antibodies that recognize different epitopes unique to the human cTnI isoform. The cTnI assay has no detectable cross reactivity with human skeletal muscle troponin I. By this method, the serum cTnI level in a normal healthy population is $\leq$0.03 ng/ml, as compared with $\leq$0.4 ng/ml by the conventionally used Stratus II fluorometric enzyme immunoassay (Dade International, Miami, Florida). Creatine kinase, MB isoenzymes were measured with the ACCESS CK-MB assay (Sanofi Diagnostic Pasteur). The ACCESS CK-MB assay is a two-site sandwich immunochemiluminescent assay using two mouse monoclonal antibodies that specifically recognize CK-MB. By this method, the reference normal limit of CK-MB is $\leq$4 ng/ml.

The analytical sensitivity of each assay was defined as the smallest concentration that can be distinguished from zero. Ten replicates of the zero calibrator were run for cTnI and CK-MB. The analytical sensitivity was calculated using the 10-zero calibrator replicate relative light units measured 2 SD from the zero-curve fit. Both assays generated analytical sensitivity values within package-insert specifications; the analytical sensitivity of cTnI was 0.006 ng/ml, against an expected value of 0.03 ng/ml, and that of CK-MB was 0.09 ng/ml, against an expected value of 0.3 ng/ml. The precision within runs was calculated based on 10 replicates of BioRad's tri-level cardiac control. The procedure adopted included one analyte per tray, three control levels per analyte and 10 replicates per control level. The imprecision within runs for both assays was $<$10%.

Serum concentrations of creatinine, calcium, potassium, sodium, albumin, bicarbonate, chloride and blood urea nitrogen were measured on a Hitachi 747 Analyzer (Hitachi, Indianapolis, Indiana), using routine methods according to the manufacture's protocols.

Follow-up. The study group was classified into two groups according to the pre-dialysis serum cTnI level on initial enrollment: 1) patients with normal serum cTnI levels ($\leq$0.03 ng/ml); and 2) patients with elevated serum cTnI levels ($>$0.03 ng/ml). All patients were followed up for two years from the time of their initial enrollment in the study. The end points studied were: 1) all-cause mortality; 2) cardiac mortality; 3) all-cause hospital admissions; and 4) cardiac hospital admissions. Hospital records, outpatient clinic records and interviews with the patient, family or primary physician were used for confirmation of the events. In case of death, the cause of death was verified by reviewing medical records or death certificates. Death due to acute myocardial infarction, pulmonary edema, cardiogenic shock or malignant arrhythmias was deemed cardiac. Sudden unexplained death was also considered as cardiac. Admission secondary to acute myocardial infarction, chest pain suggestive of an acute coronary syndrome, congestive heart failure, arrhythmias and vascular diseases were considered as cardiac. Admissions related to vascular access for dialysis were not included in the admission counts.

Statistical analysis. Continuous variables were expressed as the mean value $\pm$ SD and were analyzed by the Student *t* test. Categorical variables were expressed as percentages and were analyzed by the chi-square or Fisher exact test, as appropriate. A two-tailed p value $\leq$0.05 was considered significant. Kaplan-Meier survival analysis was performed to

Table 1. Baseline Clinical Characteristics: Comparison Between Patients With Normal cTnI Levels and Those With Elevated Levels

Characteristics	Normal cTnI (n = 102)	Elevated cTnI (n = 24)
Age (yrs)	59.0 ± 15.4	62.2 ± 14.5
Gender		
Male	63 (62%)	14 (58%)
Female	39 (38%)	10 (42%)
Hypertension	84 (82%)	21 (88%)
Diabetes	44 (43%)	10 (42%)
Congestive heart failure	27 (26%)	7 (29%)
Previous myocardial infarction	13 (13%)	3 (12%)

Data are presented as the mean value ± SD or number (%) of patients. p = NS for all characteristics compared between the two groups.
cTnI = cardiac troponin I.

Table 2. Baseline Serum Biochemical Profile: Comparison Between Patients With Normal cTnI Levels and Those With Elevated Levels

Serum Biochemicals	Normal cTnI (n = 102)	Elevated cTnI (n = 24)	p Value
Albumin (g/dl)	3.81 ± 0.36	3.81 ± 0.38	0.98
Bicarbonate (mEq/l)	20.1 ± 2.62	20.0 ± 2.33	0.96
Blood urea nitrogen (mg/dl)	64.2 ± 20.8	63.8 ± 21.9	0.93
Calcium (mg/dl)	8.93 ± 0.95	9.06 ± 0.81	0.52
Chloride (mEq/l)	98.3 ± 4.23	99.0 ± 3.70	0.41
CK-MB (ng/ml)	3.27 ± 1.85	4.18 ± 2.25	0.04
Creatinine (mg/dl)	10.30 ± 3.10	9.25 ± 3.99	0.17
Potassium (mEq/l)	4.77 ± 0.67	4.71 ± 0.90	0.73
Sodium (mEq/l)	135.8 ± 3.61	137.1 ± 2.69	0.09

Data are presented as the mean value ± SD.
CK-MB = creatine kinase-MB isoenzyme; cTnI = cardiac troponin I.

evaluate significant differences in all-causes death and cardiac death between patients with normal cTnI levels and those with elevated cTnI levels. Receiver-operating characteristic (ROC) curves of serum cTnI, as a predictor of all-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions, were plotted. Logistic regression analysis was performed to identify independent predictors of all-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions. Cox regression analysis was used to determine independent variables as the best predictors of time to death. All of the statistical analyses were performed using SPSS, version 7.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Two patients received a kidney transplant during the study period; therefore, they were not included in the analysis. Of the other 126 patients, 102 had serum levels of cTnI within normal limits (≤0.03 ng/ml) and 24 had elevated levels (>0.03 ng/ml). The serum cTnI values in the group of patients with normal levels ranged from 0 to 0.029 ng/ml (mean [±SD] 0.015 ± 0.007 ng/ml), and the serum cTnI values in the group of patients with elevated levels ranged from 0.031 to 0.14 ng/ml (mean [±SD] 0.053 ± 0.029 ng/ml; $p < 0.0001$). There was no significant difference in baseline clinical characteristics between the patients with normal cTnI levels and those with elevated cTnI levels (Table 1). Similarly, there was no significant difference in the baseline biochemical profile between the two groups, except for a high CK-MB value in the group with elevated cTnI (Table 2).

Twenty patients (20%) in the normal cTnI group and four (17%) in the elevated cTnI group died during the two-year follow-up period. Of the 20 deaths in patients with normal cTnI, four (20%) were of cardiac origin. Of the four deaths in patients with elevated cTnI, one (25%) was of cardiac origin. There was no significant difference in all-cause mortality and cardiac mortality between the two groups (Table 3). The causes of cardiac death in the patient group with normal cTnI were myocardial infarction (n = 2), congestive heart failure (n = 1) and sudden cardiac death (n = 1). The only cardiac death in the patient group with elevated cTnI was due to myocardial infarction.

The total number of all-cause hospital admissions in the normal cTnI group was 177 (mean [±SD] 1.74 ± 1.72 admissions per patient), and the total number of all-cause admissions in the elevated cTnI group was 30 (mean [±SD] 1.25 ± 1.19 admissions per patient; p = NS). The numbers of cardiac admissions were 53 (mean [±SD] 0.52 ± 0.89 admissions per patient) and 8 (mean [±SD] 0.33 ± 0.76 admissions per patient) in the normal and elevated cTnI groups, respectively (p = NS) (Table 3).

Kaplan-Meier survival analysis showed no significant differences in all-cause mortality ($p = 0.7292$ by the log-rank statistic) or cardiac mortality ($p = 0.2319$ by the log-rank statistic) between patients with normal cTnI levels and those with elevated cTnI levels. The ROCs of serum cTnI as a predictor of all-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions are shown in Figures 1, 2, 3 and 4. The data points on all of these ROC plots are near 45°, indicating that serum cTnI is not a useful tool for predicting any of these end points. Independent predictors of death were older age (65.9 ± 11.5 vs. 58.1 ± 15.7 years in dead vs. alive patients;

Table 3. Deaths and Hospital Admissions: Comparison Between Patients With Normal Cardiac Troponin I Levels and Those With Elevated Levels

End Point	Normal cTnI (n = 102)	Elevated cTnI (n = 24)
All-causes deaths	20 (20%)	4 (17%)
Cardiac deaths	4 (20%)	1 (25%)
All-cause admissions		
Total	177	30
Per patient	1.74 ± 1.72	1.25 ± 1.19
Cardiac admissions		
Total	53	8
Per patient	0.52 ± 0.89	0.33 ± 0.76

Data are presented as the number (%) of patients or number and mean value ± SD of admissions. p = NS for all end points compared between both groups.
cTnI = cardiac troponin I.

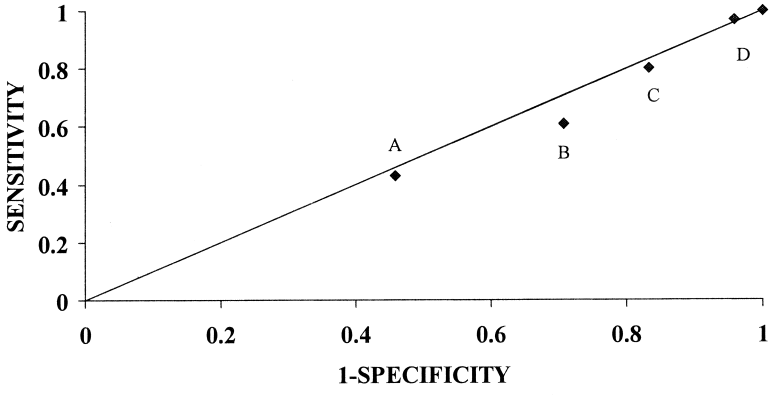

Figure 1. Receiver-operating characteristic plots of serum cardiac troponin I (cTnI) as a predictor of all-cause death.

p = 0.008 by the independent *t* test) and lower serum albumin levels (3.64 ± 0.32 vs. 3.85 ± 0.36 g/dl in dead vs. alive patients; p = 0.01 by the independent *t* test). There was no difference in the serum cTnI levels between patients who died and those who survived (0.022 ± 0.019 vs. 0.022 ± 0.021 ng/ml; p = 0.925). In logistic regression analysis, serum cTnI was not an independent predictor of all-cause mortality, cardiac mortality, all-cause hospital admissions or cardiac hospital admissions. Serum albumin was the best predictor of all-cause mortality (the lower levels were associated with higher mortality), and a history of myocardial infarction was the best predictor of cardiac mortality. The serum sodium level was an independent predictor of all-cause hospital admissions (lower levels were associated with more admissions). Hypertension and previous myocardial infarction were independent predictors of cardiac hospital admissions. The best predictors of the time to death by Cox regression analysis were age (older) ($p < 0.005$) and serum sodium level (lower) ($p < 0.005$), irrespective of the serum cTnI levels.

DISCUSSION

Study findings. The present study demonstrates that cTnI has limited prognostic significance in asymptomatic patients with chronic renal failure. All-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions were not more prevalent in patients with chronic renal failure with elevated serum cTnI levels than in patients with normal levels of serum cTnI. Serum cTnI is not a useful tool for predicting all-cause mortality, cardiac mortality, all-cause hospital admissions and cardiac hospital admissions. Cardiac TnI was not an independent predictor of all-cause or cardiac mortality; rather, older age and lower serum albumin levels were independent predictors of all-cause mortality, and a history of myocardial infarction was an independent predictor of cardiac mortality. Similarly, cTnI was not an independent predictor of all-cause or cardiac hospital admissions; rather, a lower serum sodium level was an independent predictor of all-cause hospital admissions, and hypertension and previous myocardial in-

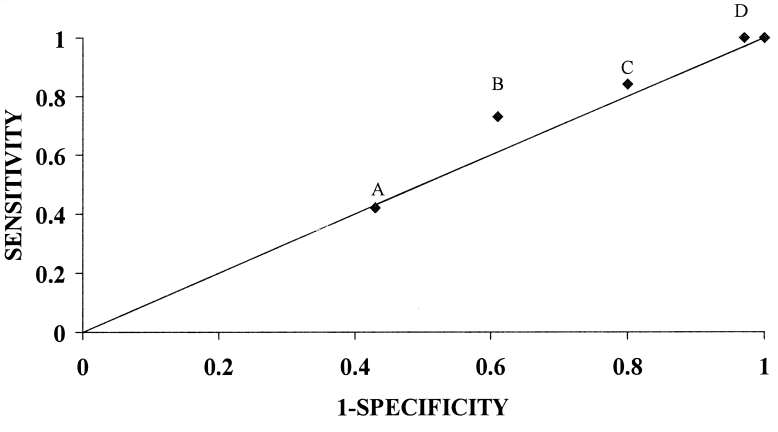

Figure 2. Receiver-operating characteristic plots of serum cardiac troponin I (cTnI) as a predictor of cardiac death.

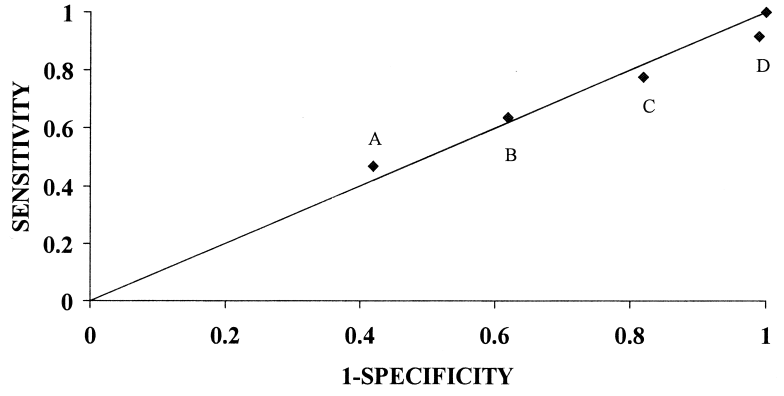

Figure 3. Receiver-operating characteristic plots of serum cardiac troponin I (cTnI) as a predictor of all-cause hospital admissions.

farction were independent predictors of cardiac hospital admissions.

Elevation of cTnI in renal failure. Although cTnI has been considered the most specific among the currently available biochemical markers of myocardial damage, its value in the presence of chronic renal failure has been questioned (28,30,32). The cause of nonspecific elevation of cTnI is not clear. The current hypotheses addressing such elevation in chronic renal failure include microinjury to the myocardium that is undetected by conventional cardiac imaging, cardiotoxicity due to changes in osmolarity and/or ion fluxes, increased cardiac preload and myocardial stretch due to volume overload and nonischemic cardiac injury due to calcium and oxalate deposition in the heart (30,32). There is little evidence to suggest that the false-positive rate of cTnI is related to the magnitude of renal insufficiency, because no relationship between the serum cTnI concentration and the serum creatinine value or creatinine clearance rate has been demonstrated, and no significant differences has been found between pre- and post-dialysis values of serum cTnI (28–30,33).

Although the reason for the elevation in serum cTnI in patients with renal disease is not clear, it may represent the problems in standardization of cTnI assays. Up to 20-fold variation in cTnI mass determination may be observed for a given patient sample when measured by different systems (34). The manufacturers quote different assay cut-off points and different studies using the same manufacturer's assay have used different cut-off points (4,17). The heterogeneous nature and biochemical complexity of the serum forms of cTnI and the difference in the epitome recognition by different methods have also hindered the standardization of

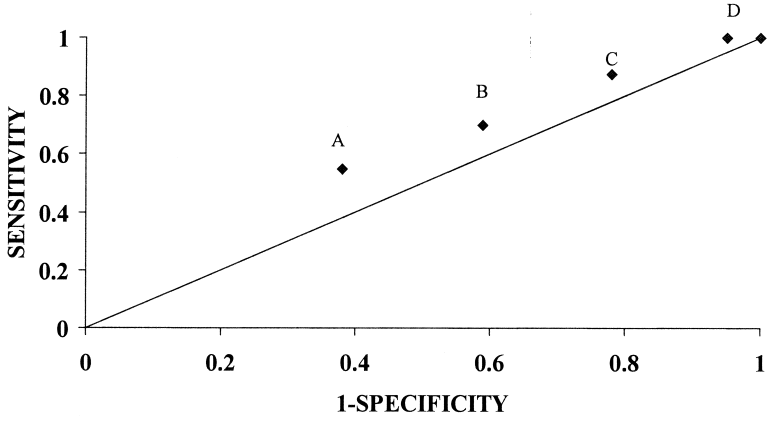

Figure 4. Receiver-operating characteristic plots of serum cardiac troponin I (cTnI) as a predictor of cardiac hospital admissions.

serum cTnI assays (34). Consequently, significant ambiguity often exists in the clinical interpretation of serum cTnI levels. Furthermore, recent studies have shown differential stability of cTnI with cTnI-troponin C complexes, which may also affect the assay results (35). In addition, binding sites of test antibodies could be altered due to changes in protein kinase C properties in patients with renal disease, because protein kinase C phosphorylates troponin I at many different sites (35).

Cardiac troponin I and prognosis. Although troponin I is a part of the troponin-tropomyosin complex of the contractile apparatus in myocytes, the exact nature of its release from the contractile apparatus of the striated muscle is not fully understood; probably it is released from the cytosolic pool into the circulation after necrosis (19). Because cTnI does not normally circulate in the blood, or circulates only in minute amounts, and is 13 times more abundant in the myocardium than is CK-MB, on the basis of weight, the signal-to-noise ratio associated with cTnI is much more favorable for the detection of minor amounts of cardiac necrosis (36). Elevation of cTnI has been shown to be an important factor for the short- and long-term prognoses of cardiac mortality and nonfatal cardiac events in patients with unstable angina (7). As more research is focused on the clinical utility of cTnI, its role as a prognosis indicator is expanding. It has been shown that elevated cTnI in acute myocardial infarction predicts lower reperfusion rates and an increased risk of primary angioplasty failure (37). Furthermore, it can identify a group of patients with acute coronary syndromes who would benefit from early catheter-based coronary interventions (38). Cardiac troponin I has also been shown to identify a subgroup of patients who are at high risk of graft failure after cardiac transplantation; thus, it may be used in the early detection of rejection-related myocardial injury/necrosis (39). Although not proven conclusively, microinjury to the myocardium is a frequently proposed mechanism for elevation of troponins in the absence of clinical, ECG or echocardiographic abnormalities. Histologic findings strongly suggest that minor myocardial cell injury takes place more frequently in high-risk groups of patients who have a worse prognosis (4,6,40).

Cardiac troponin I and prognosis in renal failure. Although there have been a few previous reports on the ability of cTnI to predict future cardiac events in patients with chronic renal failure who are free of cardiac symptoms, the published data are sparse and the follow-up periods have been short (29–31). These studies have demonstrated mixed results. Apple et al. (29) retrospectively studied 16 patients receiving long-term hemodialysis to evaluate the prognostic significance of both cTnI and cTnT over a period of one year. All of these patients had type I diabetes for a mean period of 24 years. The end point evaluated was the occurrence of fatal myocardial infarction. The assay used to measure serum cTnI was enzyme-linked immunosorbent assay, and the upper reference limit used was of 0.8 μg/l (ng/ml). At the time of enrollment, three patients had serum cTnI levels above the upper reference limit (1.2, 2.4 and 1.6 μg/l) and 12 patients had serum cTnT levels above the upper reference limit. All three patients with elevated serum cTnI levels had a history of ischemic heart disease (unstable angina/coronary artery bypass graft [n = 1], myocardial infarction [n = 1] and unstable angina [n = 1]). Patients who had elevated cTnI levels also had elevated cTnT and CK-MB. During one-year follow-up, four patients had a fatal myocardial infarction, including those three with elevated serum cTnI levels; however, it was not analyzed whether cTnI was an independent predictor of the fatal myocardial infarction.

In another study, Mockel et al. (30) evaluated the prognostic significance of cTnI and cTnT in 40 patients with chronic renal failure. Twenty of these patients had pre–end-stage renal disease and another 20 had end-stage renal disease and were treated with hemodialysis. Patients with any symptoms of angina pectoris during the two weeks before enrollment or an acute coronary syndrome in the four weeks before enrollment were not included in the study. Serum cTnI was measured by immunofluorescence assays made by two different manufacturers—Dade Stratus II (Dade International) and Behring OPUS Plus (Behring Diagnostics, Frankfurt, Germany). The cTnI cut-off values used in this study were 0.4 μg/l (ng/ml) for the Dade Stratus II assay and 1.6 μg/l (ng/ml) for the Behring OPUS Plus assay. In patients with pre–end-stage renal disease, 20% of patients had elevated cTnI levels by the Dade Stratus II assay and 10% by the Behring OPUS Plus assay, and in patients with end-stage renal disease treated with hemodialysis, these rates were 55% and 15%, respectively. Most of these elevated levels were modest. The follow-up period was nine months. The primary end points studied were acute myocardial infarction, all-cause mortality and hospital admission. One patient had an acute myocardial infarction, 5 patients died and 22 patients were admitted to the hospital during the nine-month follow-up period. The logistic regression model showed that serum cTnI measured by any assay was not a predictor of any of the primary end points, considered individually or in combination of two or all three end points.

In a pilot study, Ropollo et al. (31) examined the usefulness of cTnI and cTnT as predictors of subsequent cardiac events in 49 patients with chronic renal failure treated with dialysis (48 on hemodialysis and 1 on peritoneal dialysis). An additional 83 patients with renal failure who were not on dialysis were also examined. Serum cTnI was measured by the Behring OPUS immunofluorescence assay, and the cut-off value used was 0.5 ng/ml. The end points evaluated were unstable angina, acute myocardial infarction and cardiac death. The follow-up period was six months. Among the 49 dialysis patients, three had elevated cTnI at entry (0.94, 1.34 and 14.5 ng/ml). Six patients had significant cardiac events (myocardial infarction [n = 4], arrhythmia [n = 1] and unstable angina [n = 1]) during the

six-month follow-up period. Of these six patients, three had elevated cTnI serum levels, but the other three had normal cTnI serum levels. Three patients died during the six-month follow-up period. Of these, two had elevated serum levels of cTnI. All three patients with elevated troponin I also had elevation of cTnT, and, similarly, all six patients who developed cardiac events had elevation of cTnT. All 49 patients on dialysis, although asymptomatic at the time of enrollment, were had chronic stable angina. Other comorbid conditions reported in this group of patients were hypertension (n = 46), previous myocardial infarction (n = 10), congestive heart failure (n = 10), diabetes (n = 22), hyperlipidemia (n = 13) and arrhythmias (n = 6). Of the 83 patients with renal failure who were not on dialysis, two had elevated cTnI, but neither of them had any adverse cardiac events or died during the six-month follow-up period, and two patients had myocardial infarction, but neither of them had elevated troponin I levels. Logistic regression analysis was not performed to determine whether cTnI was an independent predictor of acute myocardial infarction, unstable angina or cardiac death.

In the present study, in which patients with chronic stable angina were not included, we examined 126 patients with end-stage renal disease treated with long-term hemodialysis and prospectively followed for two years for mortality and hospital admissions. Mortality in patients with chronic renal failure and elevated cTnI was compared with that in patients with chronic renal failure and normal cTnI by Kaplan-Meier survival analysis, and no difference was found between the two groups. The ROC plots failed to demonstrate serum cTnI as a useful tool for predicting any of the end points. In addition, logistic regression analysis was used to examine the independent predictive value of cTnI for all four end points, and it was found that cTnI was not an independent predictive of any end point. Older age and lower serum albumin levels were independent predictors of all-cause mortality, whereas a history of myocardial infarction was an independent predictor of cardiac mortality. A lower serum sodium level was an independent predictor of all-cause hospital admissions, whereas hypertension and previous myocardial infarction were independent predictors of cardiac hospital admissions. Moreover, Cox regression analysis showed that the cTnI level was not predictive of the time to death; rather, older age and lower serum sodium levels were predictive of the time to death.

Study limitations. Unstable angina and acute myocardial infarction were not used as study end points. The diagnosis of unstable angina is purely subjective, and the diagnosis of acute myocardial infarction in patients with chronic renal failure may remain uncertain because of the more ambiguous symptoms and the presence of abnormal baseline ECGs in a number of these patients. The biochemical diagnosis of acute myocardial infarction is also often difficult in these patients because of the frequent false-positive elevations of the cardiac markers. Therefore, the study protocol was limited to the definitive end points of death and hospital admissions.

Conclusions. Cardiac troponin I has a limited role in predicting future mortality and hospital admissions in asymptomatic, ambulatory patients with chronic renal failure treated with long-term hemodialysis. The findings of this study should not be extrapolated to patients with chronic renal failure who have cardiac symptoms.

Reprint requests and correspondence: Dr. Ijaz A. Khan, Cardiac Center, Creighton University, 3006 Webster Street, Omaha, Nebraska 68131. E-mail: ikhan@cardiac.ctrighton.edu.

REFERENCES

1. Adams JE, Bodor GS, Davilla-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. Circulation 1993;88: 101–6.
2. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337:1648–53.
3. Morrow DA, Rifai N, Tanasijevic MJ, Wybenga DR, de Lemos JA, Antman EM. Clinical efficacy of three assays for cardiac troponin I for risk stratification in acute coronary syndromes: a Thrombolysis In Myocardial Infarction (TIMI) 11-B substudy. Clin Chem 2000;46: 453–60.
4. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–449.
5. Ohman EM, Armstrong PW, Christenson RH. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996;335:1333–41.
6. Luscher MS, Thygesen K, Ravkilde J, Heickendorff L, for the TRIM Study Group. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary disease. Circulation 1997;96:2578–85.
7. Galvani M, Ottani F, Ferrini D, et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina Circulation 1997;95:2053–9.
8. Antman EM, Tanasijevic MJ, Cannon CP, et al. Cardiac troponin I on admission predicts death by 42 days in unstable angina and improved survival with an early invasive strategy: results from TIMI-IIIB (abstr). Circulation 1995;Suppl I:I663.
9. NIH consensus statement: morbidity and mortality of renal dialysis. Ann Intern Med 1994;121:62–70.
10. Jaffe As, Ritter C, Meltzer V, Harter H, Roberts R. Unmasking artifactual increases in creatine kinase isoenzymes in patients with renal failure. J Lab Clin Med 1984;104:193–202.
11. Green TR, Golper TA, Swenson RD, Pulliam JP, Morris CD. Diagnostic value of creatine kinase and creatine kinase MB isoenzyme in chronic hemodialysis patients: a longitudinal study. Clin Nephrol 1986;25:22–7.
12. Ma KW, Brown DC, Steele BW, From AH. Serum creatine kinase MB isoenzyme activity in long-term hemodialysis patients. Arch Intern Med 1981;141:164–66.
13. Lal SM, Nolph KD, Hain H, et al. Total creatine kinase and isoenzyme fractions in chronic dialysis patients. Int J Artif Organs 1987;10:72–6.
14. Medeiros LJ, Schotte D, Gerson B. Reliability and significance of increased creatine kinase MB isoenzyme in the serum of uremic patients. Am J Clin Pathol 1987;87:103–8.
15. McLaurin MD, Apple FS, Herzog CA, Sharkey SW. Cardiac troponin I, T, and CK-MB in chronic hemodialysis patients (abstr). Circulation 1995:92 Suppl I:I80.
16. McLaurin MD, Apple FS, Voss EM, Herzog CA, Sharkey CW. Cardiac troponin I, cardiac troponin T and creatine kinase MB in dialysis patients without ischemic heart disease: evidence of cardiac troponin T expression in skeletal muscle. Clin Chem 1997;43:976–82.

17. Hafner G, Thome-Kromer B, Schaube J, et al. Cardiac troponins in serum in chronic renal failure. Clin Chem 1994;40:1790–1.
18. Croltoru M, Taegtmeyer H. Spurious rises in troponin T in end-stage renal disease. Lancet 1995;346:974.
19. Frankel WL, Herold DA, Ziegler TW, Fitzgerald RL. Cardiac troponin T is elevated in asymptommatic patients with chronic renal failure. Am J Clin Pathol 1996;106:118–23.
20. Bhayana V, Gougoulias T, Cohoe S, Henderson R. Discordance between results for serum troponin T and troponin I in renal disease. Clin Chem 1995;41:312–7.
21. Li D, Keffer J, Corry K, Vazquez M, Jialal I. Nonspecific elevation of troponin T levels in patients with chronic renal failure. Clin Biochem 1995;28:474–7.
22. Collinson PG, Stubbs PJ, Rosalki SB. Cardiac troponin T in renal disease. Clin Chem 1995;4:1671–3.
23. Wilkinson JM, Grand RJ. Comparison of amino acid sequence of troponin I from different striated muscles. Nature 1978;271:31–5.
24. Saggin L, Gorza L, Ausoni S, Schiaffino S. Troponin switching in the developing heart. J Biol Chem 1989;264:16299–302.
25. Bhavsar P, Dhoot GK, Cumming DVE, Butler-Browne GS, Yacoub MH, Barton OJR. Developmental expression of troponin I isoforms in fetal human heart. FEBS Lett 1991;292:5–8.
26. Bodor GS, Porterfield D, Voss EM, Smith S, Apple FS. Cardiac troponin I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. Clin Chem 1995;41:1710–5.
27. Van Lente F, McErlean ES, DeLuca SA, Peacock F, Rao JS, Nissen SE. Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: a case-matched study. J Am Coll Cardiol 1999;33:471–8.
28. Tun A, Khan IA, Win MT, et al. Specificity of cardiac troponin I and creatine kinase-MB isoenzyme in asymptomatic long-term hemodialysis patients and effect of hemodialysis on these cardiac markers. Cardiology 1998;90:280–5.
29. Apple FS, Sharkey SW, Hoeft P, et al. Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: a 1-year outcomes analysis. Am J Kidney Dis 1997;29:399–403.
30. Mockel M, Schindler R, Knorr L, et al. Prognostic value of cardiac troponin T and I elevations in renal disease patients without acute coronary syndromes: a 9-month outcome analysis. Nephrol Dial Transplant 1999;14:1489–95.
31. Roppolo LP, Fitzgerald R, Dillow J, Ziegler T, Rice M, Maisel A. A comparison of troponin T and troponin I as predictors of cardiac events in patients undergoing chronic dialysis at a Veteran's Hospital: a pilot study. J Am Coll Cardiol 1999;34:448–54.
32. Khan IA, Tun A, Wattanasuwan N, et al. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. Am J Emerg Med 1999;17:225–9.
33. Collinson PO, Hadcocks L, Foo Y, et al. Cardiac troponins in patients with renal dysfunction. Ann Clin Biochem 1998;35:380–6.
34. George SK, Singh AK. Current markers of myocardial ischemia and their validity in end-stage renal disease. Curr Opin Nephrol Hypertens 1999;8:719–22.
35. Jideama NM, Noland TA, Raynor RL, et al. Phosphorylation specificities of protein kinase C isoenzymes for bovine cardiac troponin I and troponin T and sites within these proteins and regulation of myofilament properties. J Biol Chem 1996;271:23277–83.
36. Adams JE III, Schechtman KB, Landt Y, Landenson JH, Jaffe AS. Comparable detection of acute myocardial infarction by creatine kinase MB isoenzyme and cardiac troponin I. Clin Chem 1994;40:1291–5.
37. Matetzky S, Sharir T, Domingo M, et al. Elevated troponin I level on admission is associated with adverse outcome of primary angioplasty in acute myocardial infarction. Circulation 2000;102:1611–6.
38. Fuchs S, Kornowski R, Mehran R, et al. Cardiac troponin I levels and clinical oucomes in patients with acute coronary syndromes: the potential role of early percutaneous revascularization. J Am Coll Cardiol 1999;34:1704–10.
39. Labarrere CA, Nelson DR, Cox CJ, Pitts D, Kirlin P, Halbrook H. Cardiac-specific troponin I levels and risk of coronary artery disease and graft failure following heart transplantation. JAMA 2000;284:457–64.
40. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med 1992;327:146–50.